MEDICINE CABINET

Treatment advances in rheumatoid arthritis

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Rheumatoid arthritis (RA) is a chronic, often debilitating autoimmune disorder characterized by persistent synovial inflammation that leads to cartilage and bone destruction. RA afflicts over 2 million Americans and contributes to substantial morbidity and increased mortality. It is estimated that one third to one half of patients suffering from RA may have moderate to severe disease. Unfortunately, there is currently no cure for RA. Management strategies are primarily focused on reducing pain and inflammation, preserving range of motion, and slowing disease progression.

In the past, drugs often had serious side effects and limited efficacy. Over the past year, several new options have emerged for the management of RA. These products include new formulations/combinations of existing products (e.g., diclofenac/misoprostol, Arthrotec®), additional refinements to existing pharmacologic classes of medications, and new approaches that target the underlying processes that perpetuate RA. This article will highlight some of these advancements.

CELECOXIB (CELEBREX™)

Celecoxib (Celebrex™, G.D. Searle & Co, Pfizer, Inc.) was approved by the FDA in December 1998 for the relief of signs and symptoms of osteoarthritis (OA) and RA. It is the first of several non-steroidal anti-inflammatory drugs (NSAIDs) referred to as "selective" COX-2 inhibitors.

According to adverse drug reaction reports obtained under the Freedom of Information Act, celecoxib has been associated with 10 deaths and 11 cases of gastrointestinal hemorrhages since its introduction in the United States.[1] It is important, however, to emphasize that these cases have not been fully analyzed and causality has not been established.

As with many new drugs, the full safety profile of celecoxib may not be realized until it has been exposed to widespread use and additional trials are completed. At this time, the FDA has not issued any additional warnings.

Pharmacology

COX (cyclooxygenase) is the first enzyme in the prostaglandin synthesis pathway. It exists in two isoforms, COX-1 and COX-2, with COX-1 being expressed constitutively in most tissues. COX-2 exists in lower levels and is inducible by various stimuli including cytokines, mitogens, and endotoxins.[2] It is found in the brain and kidneys. The current hypothesis is that COX-2 is primarily responsible for prostaglandin synthesis in the inflammatory process whereas COX-1 is involved in prostaglandin synthesis for normal homeostasis.[3] Most NSAIDs currently available inhibit both COX-1 and COX-2. Celecoxib has a 375-fold greater affinity for COX-2.[4]

Clinical trials

Published clinical data are limited to short-term phase II trials. The results of four phase II trials were recently reported by Simon et al.[5] In a 2-week phase II OA trial comparing 40 mg, 100 mg, or 200 mg celecoxib twice daily versus placebo, celecoxib was statistically superior to placebo as evaluated by both patients and physicians. Similar results versus placebo were obtained in a 4-week RA trial comparing 40 mg, 200 mg, or 400 mg celecoxib twice daily; however, the 40 mg twice daily group failed to reach statistical significance after the first week. The remaining phase II trials consisted of an endoscopic assessment of gastrointestinal tolerance and an assessment of platelet effects. In the endoscopy trial, celecoxib and placebo produced no gastric ulcers (defined as any lesion of any size with unequivocal depth) compared to 19% of naproxen treated patients following 1 week of therapy. No meaningful effects on platelet aggregation or thromboxane B2 levels were observed following 5 days of therapy.

A summary of unpublished clinical trials is available from the manufacturers product package insert.[6] In RA trials of up to 24 weeks duration, celecoxib 100 mg or 200 mg twice daily was superior to placebo and comparable to naproxen 500 mg twice daily. In some patients, the 200 mg twice daily dose provided additional benefit; however, no additional benefit was gained with doses of 400 mg twice daily.

Pharmacokinetics

Following oral administration, peak levels are achieved at approximately 3 hours. Celecoxib may be administered without regard to meals. Celecoxib has an effective half-life of 11 hours and is eliminated by metabolism primarily via cytochrome P450 2C9. Fluconazole and other inhibitors of 2C9 may increase celecoxib levels. Celecoxib may increase lithium levels in patients on lithium therapy. Preliminary studies in normal subjects receiving warfarin did not reveal an alteration in anticoagulant effect.

Adverse events

Adverse events reported in these trials consisted of headache, diarrhea, rhinitis, nausea, sinusitis, dyspepsia, and abdominal pain. The incidence of these reactions was similar to those observed in the placebo group. Laboratory abnormalities observed in these short-term trials included isolated elevations in biliary and liver function tests.

Administration

The recommended dose of celecoxib for OA is 200 mg daily either as a single dose or in two divided doses. For RA, the recommended dose is 100 mg to 200 mg twice

daily. It is available in 100-mg and 200-mg capsules and has been priced competitively with other proprietary NSAIDs (see Table 1).

Celecoxib appears to be effective in treating OA and RA. Whether COX-2 selective NSAIDs will produce fewer episodes of serious gastrointestinal bleeding awaits further clinical trials. The FDA has taken a cautious approach. Their approval letter states, "that any advertising and/or promotional activity of this product will be considered false and/or misleading…if it presents suggestions or representations that COX-2 selectivity confers on the product any claims of safety beyond what has been demonstrated in clinical studies and presented in the approved labeling."

LEFLUNOMIDE (ARAVA™)

Leflunomide (Arava™, Hoechst Marion Roussel) is a new immunomodulatory agent approved for the treatment of active RA. It is the first oral agent to receive labeling for use in reducing signs and symptoms of RA and in retarding structural damage as evidenced by x-ray erosion and joint space narrowing. Leflunomide is structurally unrelated to other available disease-modifying anti-rheumatic drugs (DMARDs).

Pharmacology

Although the etiology of RA has not yet been fully elucidated, the role of T cells in the pathogenesis of RA has been implicated.[7] Leflunomide is thought to disrupt T-cell proliferation through the inhibition of dihydroorotate dehydrogenase, an enzyme involved in the de novo synthesis of pyridmidine.[8]

Clinical Trials

In the US/Canadian trial (unpublished data), 482 patients with active RA were randomized to treatment with leflunomide (20 mg/day), methotrexate (7.5 mg titrating to 15 mg/week), or placebo for 52 weeks.[9] Leflunomide and methotrexate were both statistically superior to placebo in reducing the signs and symptoms of RA as assessed by the primary efficacy measure, the American College of Rheumatology (ACR) 20 responder rate at study endpoint. ACR20 responder rates at endpoint were 41% for leflunomide, 35% for methotrexate, and 19% for placebo. No difference was detected between the two active groups. Mean changes in X-ray Sharp Score, a measure of structural damage resulting from disease progression, were +0.5 for leflunomide, +0.9 for methotrexate, and +2.2 for placebo.

In a supportive, non-placebo-controlled European trial (unpublished data), 999 patients with active RA were randomized to treatment with leflunomide (20 mg/day) and methotrexate (7.5 mg titrating to 15 mg/week).[9,10] At 52 weeks, both treatments produced clinically significant improvements over placebo. No difference in Sharp Score was detected.

The only published phase III study to date is a short-term placebo-controlled European trial comparing leflunomide (20 mg qd) with sulfasalazine (2 g qd).[11] Both agents were equally efficacious in reducing joint counts and improving global assessments. Radiographic assessment of disease progression was similar between the two active groups.

Overall, treatment effect of leflunomide was observed by 1 month, stabilized by 3 to 6 months, and maintained throughout course of treatment.

Pharmacokinetics

Leflunomide is a prodrug that is rapidly converted to its main active metabolite, A77 1726. This active metabolite is further metabolized and undergoes both renal and biliary excretion. The prolonged half-life of leflunomide (approximately

Table 1 *Relative cost comparison of selected agents*

Agent	Usual Dose	Estimated Cost / month (based on AWP)
Celecoxib (Celebrex™)	OA: 200 mg po qd RA: 100-200 mg po bid	$72.60 to $145.20
Naproxen (Naprosyn®) generics available	500 mg po bid	$80.40
Ibuprofen (Motrin®, Advil®) generics available	800 mg po tid	$25.20
Diclofenac/misoprostol (Arthrotec®)	OA: 50 mg/200 mg po tid	$126.00 to $168.00
	RA: 50/200 mg po tid-qid	
Leflunomide (Arava™)	20 mg po qd	$244.80
Methotrexate (Rheumatrex®) generics available	7.5 to 15 mg po weekly	$42.00 to $84.00
Etanercept (Enbrel™)	25 mg sc twice weekly	$1,100.00

2 weeks) is attributed to its high protein binding and enterohepatic recirculation.[12] Therefore, a loading dose is necessary to rapidly attain therapeutic plasma levels.

Administration of cholestyramine and activated charcoal results in rapid reduction in plasma concentration of the active metabolite (these agents may be used therapeutically to accelerate drug removal). The active metabolite of leflunomide is also noted to inhibit cytochrome P450 2C9. Plasma levels of certain NSAIDs and tolbutamide may be increased when given with leflunomide. Concomitant administration with rifampin has been shown to increase plasma levels of the active metabolite by up to 40%.

Adverse reactions

Adverse reactions observed with leflunomide therapy (from all RA trials) include diarrhea (17%), abnormal liver enzymes (5%), alopecia (10%), and rash (10%). In comparative trials, treatment-related adverse events occurred in 74-75.8% of leflunomide-treated and in 63.2-72% of methotrexate-treated patients.

Elevations in liver enzymes occurred in a significant number of patients during clinical trials although most elevations were mild and transient. Marked elevations (>3 × ULN) were rare and resolved with dose reduction or treatment discontinuation. A baseline liver function test be performed and followed monthly at the onset of therapy, then if stable, at intervals determined by the individual clinical situation. Preliminary results from a small study found the risk of hepatotoxicity to be significantly increased when dual therapy with methotrexate was utilized.[13]

Leflunomide is classified under Pregnancy Category X. Women who are or may become pregnant should avoid its use (the need for reliable contraception should be enforced for patients of childbearing age). An accelerated drug elimination procedure (cholestyramine 8 g tid for 11 days) is recommended for patients who want to become pregnant after discontinuation of leflunomide to minimize exposure to the fetus. Men wishing to father a child should also discontinue leflunomide therapy and undergo an accelerated drug elimination procedure.

Administration

Therapy should be initiated with a loading dose of 100 mg daily for 3 days. The recommended maintenance dose is 20 mg daily. While treated with leflunomide, patients may be maintained on aspirin, NSAIDs, and/or low dose corticosteroids.

Leflunomide appears to be an effective agent for the management of active of RA. Available data show comparable efficacy with methotrexate and sulfasalazine; however, it remains to be seen whether or not leflunomide demonstrates a clear clinical advantage over methotrexate, the current first-line DMARD for active RA. Additional studies are required to establish long-term clinical efficacy and safety.

ETANERCEPT (ENBREL™)

The FDA also recently approved the first biotechnology product, etanercept (Enbrel™; Immunex Corp.), for reduction in signs and symptoms of moderately to severely active RA in patients who are refractory to treatment with one or more DMARDs. It can also be used with methotrexate in patients who do not respond adequately to methotrexate alone.

Pharmacology

Etanercept is a dimeric soluble form of the TNF receptor that can bind two TNF molecules. Etanercept inhibits the binding of both TNF alpha and TNF beta to the cell-surface TNF receptor, thus inhibiting activity.[14] While the causes of RA are not fully understood, it is felt that proinflammatory cytokines such as TNF may be significant factors in its pathogenesis.

Clinical trials

Moreland et al., conducted a multicenter, randomized, double-blind trial of etanercept in 180 patients with refractory RA who had not responded to one or more of the following DMARDs: hydroxychloroquine, gold, methotrexate, penicillamine, sulfasalazine, or azathioprine.[15] A significant improvement in all measures of disease activity was achieved in patients randomized to etanercept. A clear dose-response relation in swollen/tender joint reduction at 3 months was observed, with patients receiving the highest dose level of etanercept (16 mg/m^2) having the greatest improvement (61% vs. 25%, etanercept vs. placebo, P>0.001). Seventy-five percent of patients in the highest dose group had a ≥ 20% improvement in symptoms at 3 months compared to 14% of placebo patients (P<0.001). Etanercept was also associated with reductions in pain and duration of morning stiffness, physician's and patient's global assessment, improved quality of life, and reduced ESR and C-reactive protein.

Etanercept was also evaluated as an add-on treatment in a short-term study.[16] Patients with persistent RA, despite therapy with methotrexate for at least 6 months, were randomized to treatment with etanercept-plus-methotrexate or placebo-plus-methotrexate. At 24 weeks, the combination regimen achieved significantly greater efficacy for all endpoints according to ACR response criteria. The ACR 20 responder rate was 71% for the etanercept-plus-methotrexate group and 27% for the placebo-plus-methotrexate group (P<0.001). The

response seen with this combination regimen was rapid and sustained. Injection site reactions were the only events that occurred significantly more often in the combination group; potentiation of toxicities was not observed.

Pharmacokinetics

With single subcutaneous injections, a median half-life of 115 hours (range 98 to 300 hours) was observed. Upon chronic administration, the median steady-state serum concentration was 3.0 μg/L (range 1.7 to 5.6 μg/L). These pharmacokinetic parameters did not vary with age or gender.

Adverse events

Etanercept was generally well tolerated with no dose-limiting toxicity observed. The most common adverse effects associated with etanercept administration were injection site reactions which generally did not require discontinuation. Other adverse events reported in clinical trials included mild upper respiratory tract symptoms such as cough, rhinitis, sinusitis, URI, and pharyngitis. Non-neutralizing antibodies were detected in about 16% of patients but did not correlate with clinical outcome nor adverse events. The long-term immunogenicity of etanercept remains unknown.

Administration

Etanercept is available in cartons containing four-dose trays consisting of one 25-mg single-dose vial etanercept, diluent, syringe, and alcohol wipes. The recommended adult dose is 25 mg subcutaneously given twice weekly. The cost per month of therapy is listed in Table 1.

A similar agent, infliximab (Remicade™), is also being studied in rheumatoid arthritis and may obtain FDA approval for this indication.[17] It was recently FDA-approved for the treatment of Crohn's disease. Infliximab differs from etanercept in that it is a monoclonal antibody and is administered intravenously. A potential advantage of infliximab may include less frequent intravenous administration (every 4-12 weeks), while a disadvantage may include the potential development of antichimeric antibodies and decreased efficacy with repeated doses. It is unknown what the approved dose or final cost will be for this indication.

Etanercept is the first anti-TNF product approved for the treatment of RA in patients with moderate to severe disease who have failed to respond to one or more DMARDs. It has demonstrated efficacy in decreasing symptoms of RA; however, its effect on disease progression and potential long-term effects of anti-TNF drugs has not been determined. Discontinuation of therapy results in reappearance of symptoms within one month. Similar agents may gain FDA approval in the near future. While the exact role of etanercept or other TNF inhibitors remains to be determined, they do offer a treatment alternative for patients who have failed to respond to other treatment modalities.

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capsule

Chest pain can be due to an over active esophagus The esophagus is often blamed for non cardiac chest pain and investigators from Virginia report that abnormally long contractions of the wall could be the cause of it (*Gastroenterology* 1999; 116;29-37). They used continuous endoluminal ultrasonography to record what happened before, during and after chest pains in 20 volunteers. Contractions lasting over one minute usually preceded the pain.